LAB SPEAK…READING AND UNDERSTANDING A HEPATITIS C TEST

Triscia Martin, PA
University of Utah Hospital Division of Pediatric GI/Liver Transplant

OUTLINE

- Who to screen
- Liver function tests in the setting of chronic HCV
- HCV screening tests (Ab and viral load)
- Are alpha-fetoprotein level (AFP) levels necessary?
- Treatment decisions: labs only?
- Occupational exposure, HCV and LFTs
- Case discussion
- Final Words
- Q & A

WHO SHOULD BE SCREENED?

- Persons with a history of IV or intranasal drug use
- Persons who received clotting factors prior to 1987
- Organ transplant recipient or blood transfusion prior to mid-1992
- Hemodialysis patients
- Occupational needle-stick injury patients
- Sexual contacts of persons with chronic HCV
- Persons with elevated ALT levels (some pts can have a normal ALT and chronic HCV)
- Persons with multiple sexual partners
- Persons from endemic areas (Egypt, Cameroon etc.)
- Tatooing*

You've been exposed, what now?

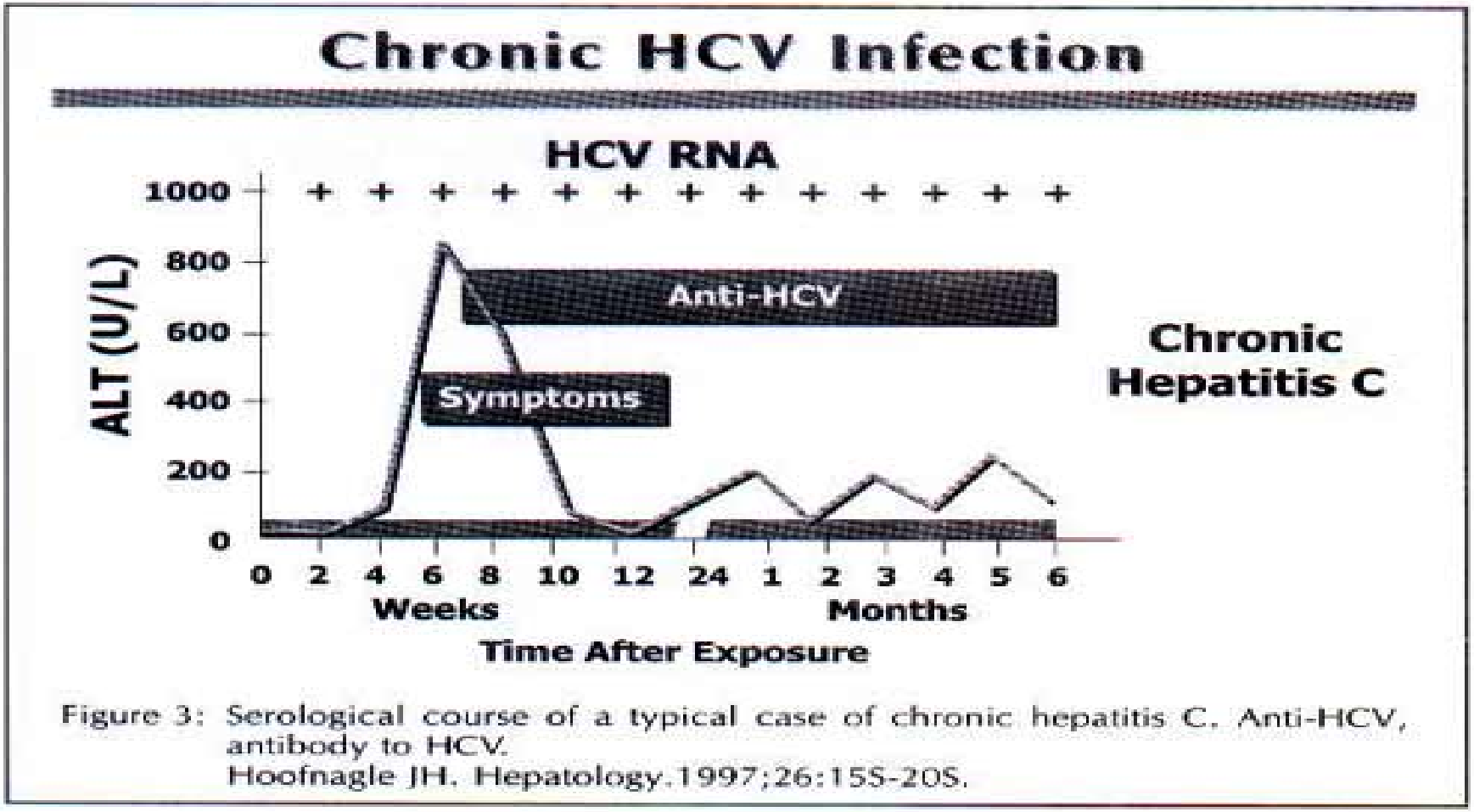


Figure 3: Serological course of a typical case of chronic hepatitis C. Anti-HCV, antibody to HCV.
Hoofnagle JH. Hepatology.1997;26:15S-20S.

SECTION 1

Interpreting LFTs in the setting of chronic HCV

ALT

- Alanine aminotransferase (SGPT)
- Found in primarily in liver
  - in smaller amounts in kidney, heart and skeletal muscle
- Usually associated with hepatic etiologies such as viral hepatitis and biliary ductal inflammation
- Most sensitive test for hepatocyte damage
- Can also be elevated in CHF, infectious mono, myopathy and strenuous exercise

IS THE ELEVATED ALT REALLY FROM THE LIVER?

- If hepatic: both AST and ALT are elevated
- If biliary problem: Alk phos & GGT also elevated
- If myopathy: CK elevated
- If infectious mono: EBV titer or Monospot will be positive

Predictive value of ALT: European Collaborative Study

- Retrospective study
- 864 pts with chronic HCV (VL +)
- 99% of all pts with an elevated ALT had F1 on biopsy; 88% had score greater than F1
- Pts with persistently normal ALT: 65% had at least F1; 26% had greater than F1 (in some cases cirrhosis)
- Degree of elevation of ALT does not indicate disease progression or predict hepatic fibrosis

Pradat P, Marcellin P et al Hepatology 2003

AST

- Aspartate Aminotransferase (SGOT)
- Associated with hepatic parenchymal damage (usually both ALT and AST elevated)
- **Two isoenzymes:** *GOT1* and *GOT2;*
- *GOT 1:* found mostly in the cardiac muscle, red blood cells, skeletal muscle, renal tissue and brain
- *GOT2*: found in hepatic mitochondria
- AST was a primary biomarker for acute MI (replaced by cardiac troponins)

AST : ALT RATIOS

- The ratio of AST to ALT can provide an indication as to whether the liver disease is secondary to EtOH use
- If AST/ALT < 1, then indicates a likely non-alcoholic cause (e.g. viral hepatitis, mono, ALF)
- If AST/ALT > 2, this is strongly suspicious of an alcoholic cause.
- Neither of these provide any prognostic information

ALKALINE PHOSPHATASE

- An enzyme associated with the biliary tract
- Not specific to liver; also seen in bone and placenta
- Is this from the liver or bone?
  - Check the isoenzymes: fractionates Alk phos into two → bone and liver
  - Check the GGT → if both elevated, hepatic origin

GAMMA GLUTAMYL TRANSFERASE

- Used to screen for bile duct injury
- Usually Alk phos and GGT elevated in the setting of chronic liver disease
- If the GGT level is **NORMAL** in a patient with a high Alk phos, the likely cause is bone disease
- **"Poor man's test for EtOH use":** An isolated, elevated GGT can be used to spot a chronic drinker
- GGT is elevated in about 75% of chronic drinkers
- Other causes: CHF, medications

Degree of LFT Elevation: 1st Tip

TABLE 1
Characteristics of elevated concentrations of liver enzymes

Test	Normal*	Mild†	Moderate†	Marked†
AST	11-32	<2-3	2-3 to 20	>20
ALT	3-30	<2-3	2-3 to 20	>20
ALP	35-105	<1.5-2	1.5-2 to 5	>5
GGT	2-65	<2-3	2-3 to 10	>10

Key: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

*Units for normal are U/L; normal reference ranges vary with the assay used and should be obtained from the laboratory performing the test.

†Numbers in these columns refer to multiples of the upper limits of normal for the individual enzyme.

Source: Flora KD, Keeffe EB. Significance of mildly elevated liver tests on screening biochemistry profiles. *J Insur Med.* 1990;22:206-210.

SECTION 2

HCV screening tests

HCV Antibody

- **Enzyme immunoassay (EIA) anti-HCV antibody test** (HCV Ab)→ detects antibodies to the virus
- Relatively inexpensive way to assess exposure
- Does **NOT** indicate current status
- HCV Ab may fail to develop these patient groups:
    - * Hemodialysis
    - * Immunosuppressed patients
    - * Acute HCV infection (may take up to 8 weeks)
- False positives occur in <1%

HCV Ab test is "Equivocal"

- RIBA (recombinant immunoblot assay):
- Confirmatory test used after EIA
  - Determines exposure NOT current status
  - In patients whom you suspect false positive EIA
  - "Weakly positive" HCV Ab test

* CDC guidelines 2003

HCV RNA Qualitative test

- HCV RNA (virus particles) can be detected in the blood using polymerase chain reaction (PCR) or transcription- mediated amplification (TMA)
- Can be used to document viral clearance post-IFN
- 2 commercially available tests:
  - Cobas Amplicor Hepatitis C Virus Test, version 2.0

    Lower limit of detection: 50 IU/mL
  - VERSANT® HCV RNA Qualitative Assay (Bayer Diagnostics, Tarrytown, NY) →TMA technology

    Lower limit of detection: 9.6 IU/mL.

HCV RNA Quantitative Test

- HCV Quantitative test: amount of HCV RNA detectable (measured in IU/mL) → **confirmatory test [viral load]**
- **Cobas Taqman** (Roche)
  - Level of detection: 75 IU/mL (< 1.9 log IU/mL)
- **Heptimax TMA** [available thru Quest Diagnostics] → **ultra-sensitive test**
  - Level of detection: 5 IU/mL (0.7 log IU/mL)
  - Sensitivities of the TMA assay are 96% at 5 IU/ml and 100% at 10 IU/mL
  - Clinical specificity is > 99.5%[35]

When to use an ultra-sensitive PCR

- Screening hemodialysis patients
- HIV Co-infected patients
- Infants of HCV-infected mothers*
- Recent needle-stick injury
  - **Decision to treat SHOULD NOT be based solely on the results of an ultra-sensitive PCR test except in acute HCV (3 months post-exposure)**

* Risk of transmission from infected mother to newborn is 5-6% (rates increase x 3 in the setting of HIV co-infection). No advantage for C-sxn vs. vaginal delivery

Does the patient really have Chronic HCV?

- **CHECK THE HCV PCR TEST** (viral load)
- If the test is positive, then the diagnosis of chronic HCV is made
- If the test is negative (HCV RNA < 75 IU/mL or < 50 IU/mL or < 5 IU/mL) then the patient does not have chronic HCV → **spontaneous viral clearance**
- Patients with a negative viral load (PCR test) **DO NOT** need to be treated with IFN/Ribavarin

Viral Load and Fibrosis

- Low VL: < 400, 000 IU/mL
- High VL: > 400, 000 IU/mL
- **Viral load does not correlate with degree of hepatic fibrosis**
- VL can be used to determine response to therapy in Genotype 1 patients[5,6]

SECTION 3

When is an AFP level necessary?

ALPHA-FETOPROTEIN LEVEL

- Tumor marker for hepatocellular carcinoma (HCC) screening
- Serum test elevated in cirrhosis, chronic hepatitis B and cancers (testis and ovary)
- Can be elevated in the setting of hepatic regeneration (e.g. cirrhosis)
- Sensitivity value of 21% (using AFP >100) and specificity value of 93%[18]

AFP, HCV & HCC

- Most reported cases of HCV-related HCC have cirrhosis or advanced fibrosis (Stage 3)[17]
- HCC risk per year for HCV cirrhosis pts: 1-4%/year
- Cost-effectiveness and efficacy: limit the use of AFP level for HCC screening to patients with HCV-induced cirrhosis

Di Bisceglie Hepatology 2003

SECTION 4

Can a decision to treat a patient be based solely on lab findings?

Normal LFTs in Chronic HCV

- Up to 60% of HCV-infected first-time blood donors and injection drug users have been reported to have normal LFTs[10-12]
- ALT values vary based on race, age, gender and body mass
- Biopsies of those with normal aminotransferase values have revealed bridging fibrosis or cirrhosis in 1% to 10% of cases[12-16]

CURRENT AASLD GUIDELINES

- Regardless of the level of ALT:
  - Liver biopsy should be done when the results will influence whether treatment is recommended
  - Liver biopsy is not mandatory in order to initiate therapy
- A liver biopsy may be obtained to provide information on prognosis

SECTION 5

Occupational Exposure and LFTs

NEEDLESTICK INJURY & LFTS

- HCV RNA is detectable within 1-2 weeks following exposure
- LFTs usually rise (in the setting of acute HCV) within 1-2 weeks post-exposure
- HCV Ab detectable at about 8 weeks following exposure[7-9]

NEEDLESTICK EXPOSURE

- Baseline status of source (HCV Ab)
- Person exposed:
  - Baseline HCV Ab and ALT **AND**
  - Follow-up HCV Ab (4-6 months) and ALT
  - May consider HCV RNA at 4-6 weeks

  - **MY GUIDELINES for the exposed:**
  - Baseline HCV Ab and LFTs
  - HCV RNA and repeat LFTs in 1-2 weeks

Current CDC guidelines

SECTION 6

CASE DISCUSSIONS

CASE 1

49 y/o Vietnamese male with h/o HCV Ab + presents to the office.

What's the next step?

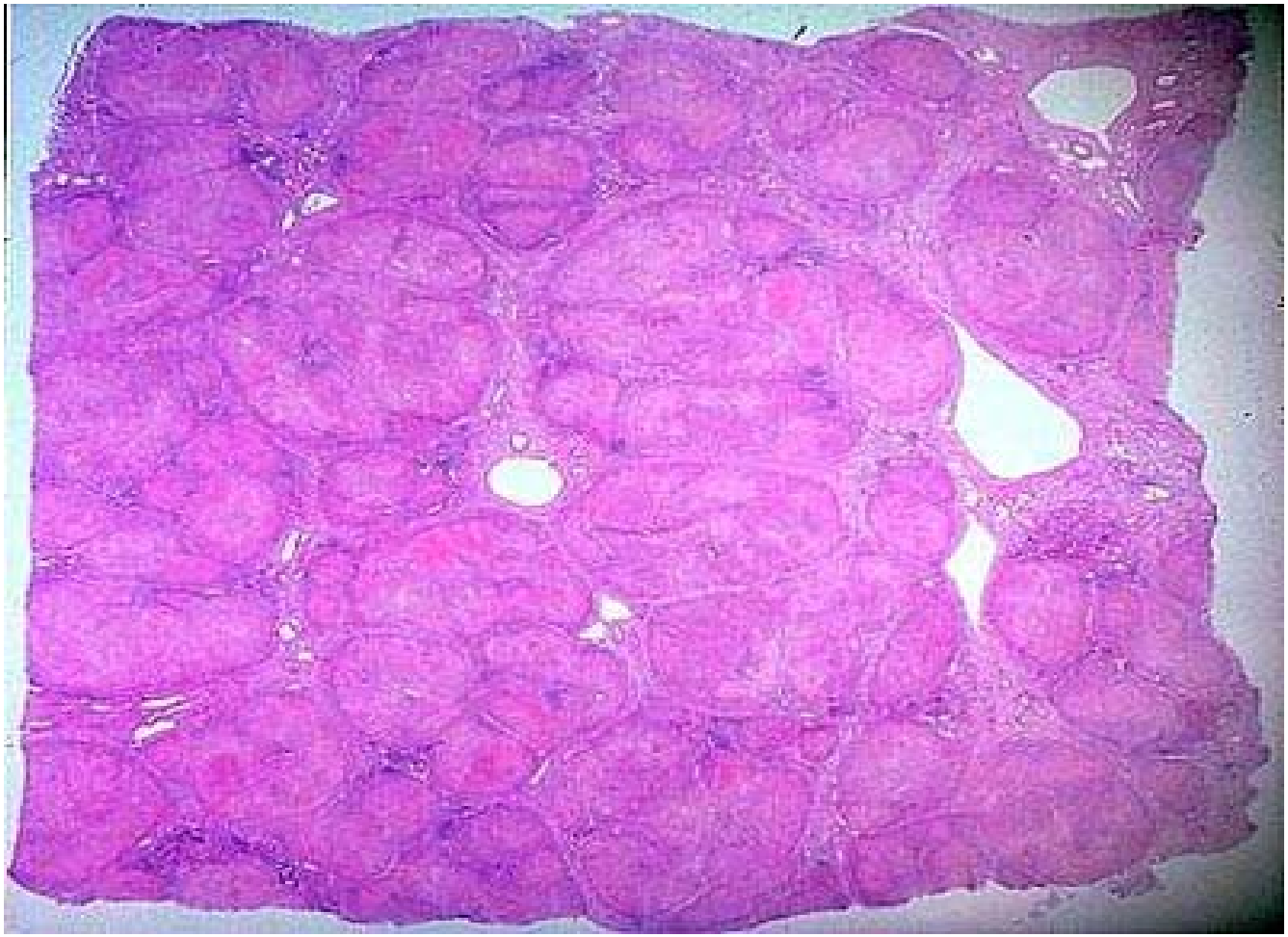
CASE 1

- History and physical
- Check LFTs (GGT included), coags, CBC w/ diff
- Check HCV viral load, genotype, Hep A and B status

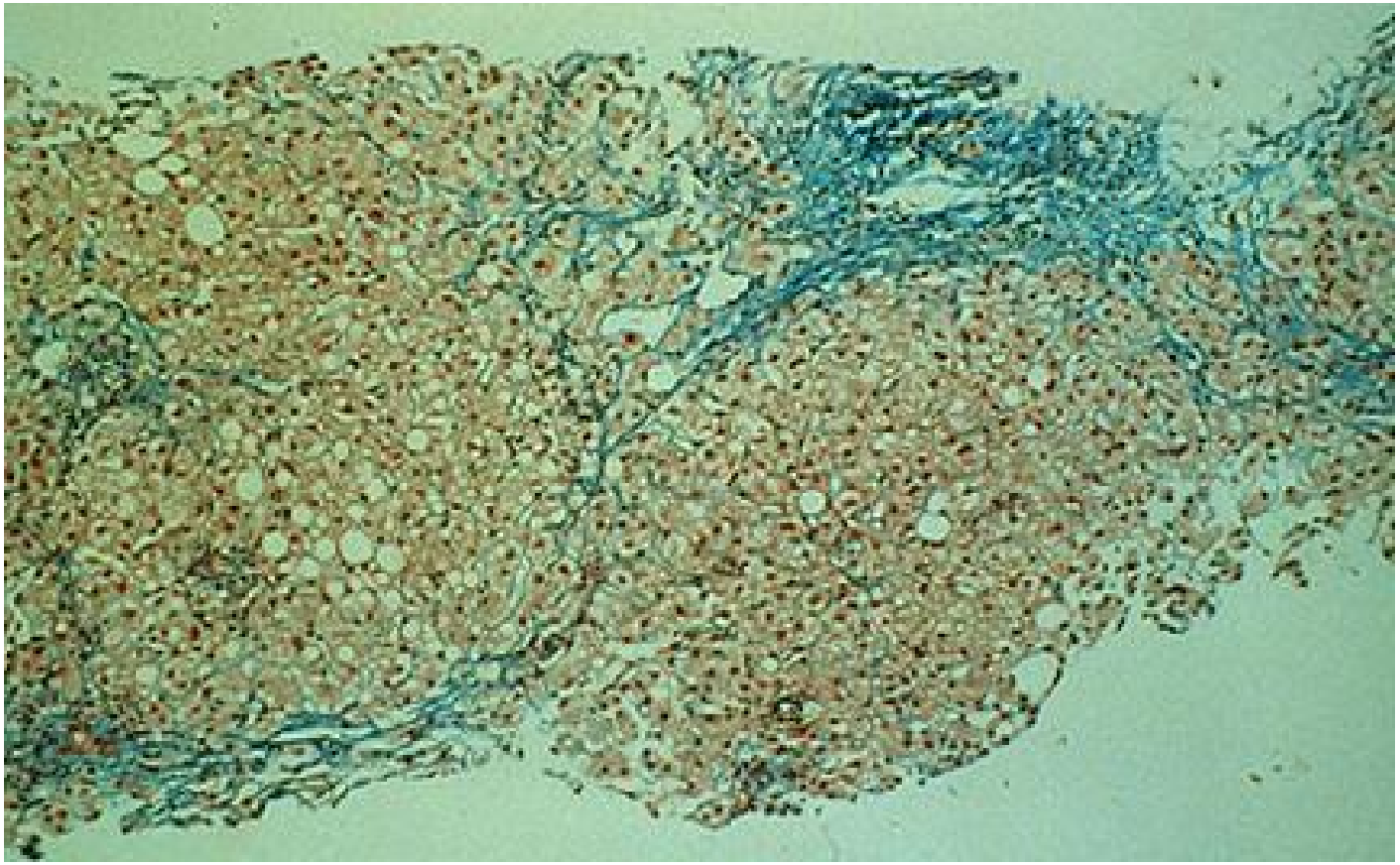
CASE 1

- Born and raised in Vietnam; migrated to US 10 years ago
- No family h/o liver dz; no h/o substance abuse
- Plts 155, AST 59, ALT 95, Alk phos 80, GGT 50, Alb 4.1, INR 1.0
- No stigmata of chronic liver disease on PE
- HCV RNA 428, 000 (5.6 log IU/mL), genotype 1b, Hep A and B naïve
- He wants to be treated, what's your advice?

LIVER BIOPSY



LIVER BIOPSY



CASE 2

- 30 y/o Native American female with 2 week history of jaundice, acholic stools and dark urine
- She admits to using IV meth in the past; last use few months ago
- Admitted to outside hosp: **4/18/06**: ALT 674, AST 767, Alk phos 187, TB 1.3, albumin 4.0, Plts 340
- **4/27/06**: Alb 3.8, TB 0.7, Alk phos 173, AST 49, ALT 167, HIV neg, Hep A and B neg, HCV Ab pos
- She is referred for treatment of chronic HCV infxn
- What's next?

CASE 2

- Re-check LFTs
- Check VL and genotype

SHE GOT LUCKY!

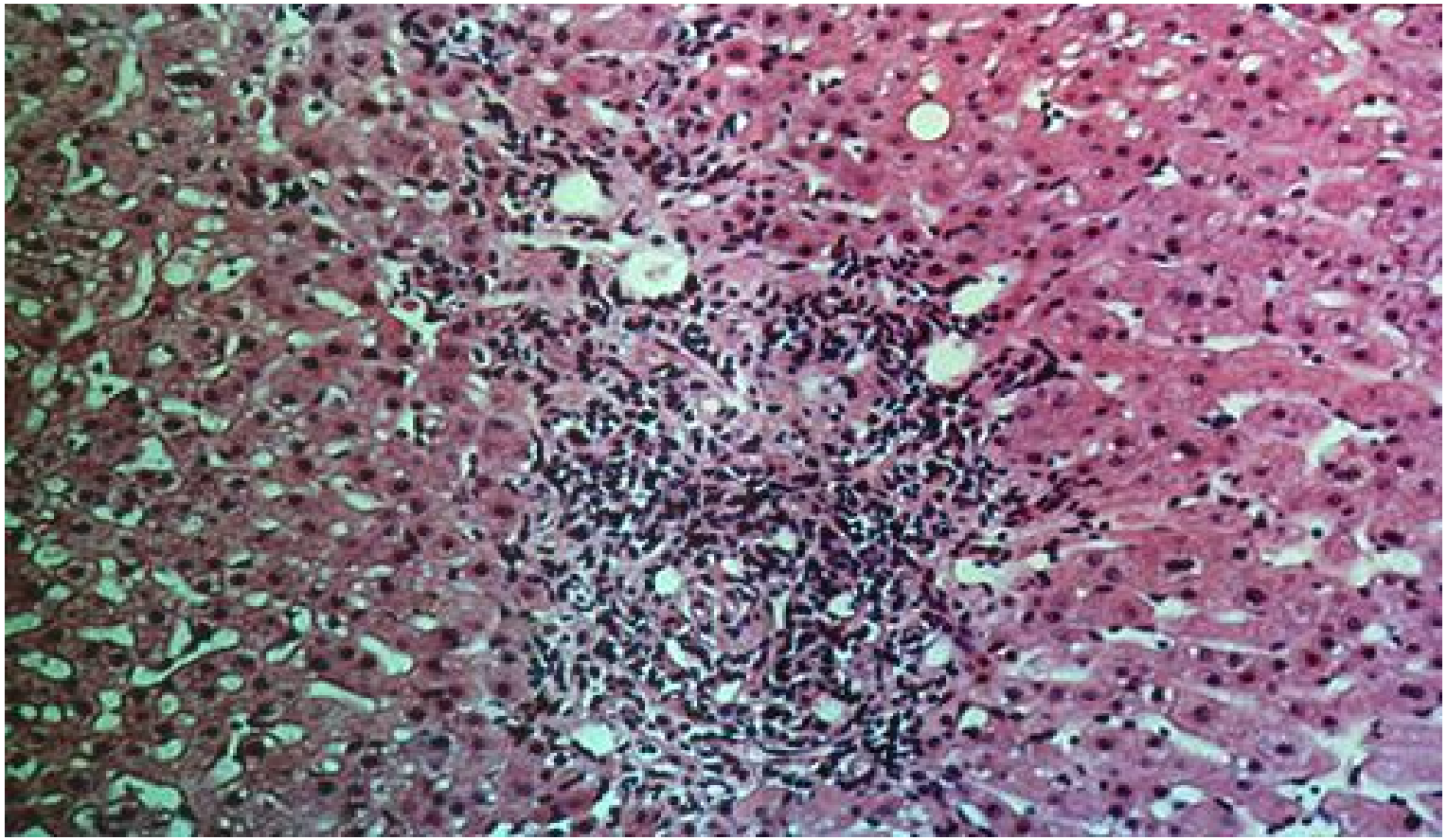
- 6/22/06: ALT 24, AST 36, Alk phos 107, TB 0.7, HCV RNA neg
- 8/3/06: LFTs still normal, HCV RNA neg*
- **Spontaneous viral clearance** –no Rx necessary [usually within the 1st month from sxs onset]
- HCV Ab will likely remain positive for her lifetime
  - * Always re-check the viral load 1 month after presumed viral clearance because some patients will have viral rebound (-ve VL to +ve VL)

CASE 3

63 year old Caucasian male with diagnosis of HCV Ab positive. LFTs normal. He is referred for evaluation.

- Has h/o MI in 5 years ago and NIDDM
- On PE → no stigmata of chronic liver dz
- HCV RNA 16, 000, 000 IU/mL
- Genotype 1a
- What's your recommendation?

HIS BIOPSY



SECTION 7

FINAL WORDS

LAST THOUGHTS

- Elevated AST & ALT are sensitive and specific for hepatic inflammation **"DO NOT IGNORE"**
- Isolated high Alk phos → check the GGT to confirm hepatic origin
- In high risk or immunosuppressed patients with HCV Ab negative
  - Check HCV Riba (tells you of exposure)
  - Check HCV RNA (viral load) which confirms the presence of viral particles

MORE LAST THOUGHTS

- Viral load does not predict risk of disease progression
  - Low viral load does not mean no fibrosis
  - High viral load does not mean cirrhosis or that HCV treatment is mandatory
- AFP levels is necessary in all patients with cirrhosis to screen for HCC
- Normal LFTs in patients with chronic HCV offers no evidence of prognosis
  - Pts with HCV-cirrhosis can have normal LFTs

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THANK YOU

ANY QUESTIONS?